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Review

SARS-CoV-2: A Piece of Bad News

SARS-CoV-2: Bir Parça Kötü Haber

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ABSTRACT

A shocking third species emerged from a family of coronaviruses (CoV) in late 2019 following viruses causing SARS (Severe Acute Respiratory Syndrome-CoV) in 2003 and MERS (Middle East Respiratory Syndrome-CoV) in 2012; it's a novel coronavirus now called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; formerly called 2019-nCoV). First emerging in China, it has spread rapidly across the globe, giving rise to significant social and economic costs and imposing severe strain on healthcare systems. Since many attempts to control viral spread has been futile, the only old practice of containment including city lockdown and social distancing are working to some extent. Unfortunately, specific antiviral drugs and vaccines remain unavailable yet. Many factors are encountered to play essential roles in viral pathogenesis. These include a broad viral-host range with high receptor binding affinity to various human tissues, viral adaptation to humans, a high percentage of asymptomatic but infected carriers, prolonged incubation, and viral shedding periods. There are also a wide variety of pulmonary and extrapulmonary tissue damage mechanisms including direct cell injury or immune-mediated damages involving the immune cells, upregulation of proinflammatory cytokines, and antibody dependent enhancement that can result in multi-organ failure. In this article, we summarise some evidence on the various steps in SARS-CoV-2 pathogenesis and immune evasion strategies to assess their contribution to our understanding of unresolved problems related to SARS-CoV-2 prevention, control, and treatment protocols.

Keywords: *SARS-CoV-2, COVID-19, pathogenesis, cytokine storm syndrome, antibody-dependent enhancement*

ÖZ

2019'un sonlarında koronavirüslerden (CoV) şok edici bir üçüncü tür, 2003'teki SARS (şiddetli akut solunum sendromu-CoV) ve 2012'deki MERS (Orta Doğu solunum sendromu-COV) peşinden geldi; şu anda şiddetli akut solunum sendromu koronavirüs 2 (SARS-CoV-2; eski adı 2019-nCoV) olarak adlandırılmaktadır. İlk olarak Çin'de ortaya çıkan, önemli ölçüde sosyal ve ekonomik maliyetlere yol açan ve sağlık sistemleri üzerinde ciddi baskılar yaratan virüs dünyada hızla yayılıyor. Viral yayılımı kontrol etmek için birçok girişim boşuna olmasına rağmen, şehirlerde sokağa çıkma kısıtlaması ve sosyal mesafe dahil olmak üzere ancak bazı eski muhafaza uygulamaları bir ölçüde işe yarıyor. Ne yazık ki spesifik antiviral ilaçlar ve aşılar henüz mevcut değildir. Viral patogenezde önemli roller oynayan birçok faktöre rastlanmaktadır. Bunlar arasında, çeşitli insan dokularına yüksek reseptör bağlanma afinitesi, insanlara viral adaptasyon, asemptomatik enfekte taşıyıcıların yüksek yüzdesi, uzun süreli inkübasyon ve uzun süreli viral bulaş periyotları ile geniş bir viral konakçı aralığı olması bulunmaktadır. Doğrudan hücre hasarı veya bağışıklık hücrelerini içeren bağışıklık aracılı hasarlar, pro-enflamatuar sitokinlerin artan regülasyonu ve çoklu organ yetmezliğine yol açabilecek antikor bağımlı geliştirmeler dahil olmak üzere çok çeşitli pulmoner ve ekstrapulmoner doku hasar mekanizmaları da bulunmaktadır. Bu makalede, SARS-CoV-2 patogenezi ve bağışıklık kaçış stratejilerindeki çeşitli adımlar hakkındaki bazı kanıtları, SARS-CoV-2 önleme, kontrol ve tedavi protokolleri ile ilgili çözülmemiş problemleri anlama konusundaki katkıları özetlemekteyiz.

Anahtar kelimeler: *SARS-CoV-2, COVID-19, patogenez, sitokin fırtınası sendromu, antikor bağımlı geliştirme*

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) belongs to Nidovirales order in the coronaviradae family, within the Betacoronavirus genus, a group of human and mammalian viruses so named due to the solar corona–like appearance of their virion surface projections under an electron microscope[1]. Coronavirus disease 2019 (COVID-19) is a newly-emerged zoonotic disease first identified following the December 2019 outbreak of atypical pneumonias in Hubei Province, Wuhan City, China[2]. It went on to become a global pandemic, with more than 2.5 million laboratory-confirmed cases and more than 170,000 deaths recorded as of April 2020 across 210 countries and territories. The issuance of a global alert by the World Health Organization (WHO) prompted containment measures to control the spread of the virus[3]. The strict restrictions on travel and commerce imposed by many countries have led to the loss of billions of dollars in economic activity.

At present, SARS-CoV-2 appears to have been transmitted to humans from animals (thought to include species of bat, snake, and pangolin)[2] raised for food and traditional medicines. Bats are currently considered the most likely hosts for SARS-CoV-2, as both have similar isolates. The SARS-CoV-2 genome is identical in 96.2% to that of the bat-CoV-RaTG13[4]. However, because there are no documented data indicating direct transmission from bats to human beings, the existence of a secondary host is likely[5]. Facts correlated to other coronaviruses may be closely pertinent in helping to understand the pathogenesis of SARS-CoV-2.

Contemporary research reports an average incubation period of 5-6 days for COVID-19, ranging from 1-14 days[6]. On average, disease symptoms develop within 11.5 days of the incubation period. COVID-19 is a lower respiratory tract disease-causing primarily mild-to-moderate symptoms, including fever, dry or productive cough, dyspnea, fatigue, sore throat, headache[7] myalgia and/or arthralgia[8]. Diarrhea is uncommon as vomiting. An estimated 50% of human infections are asymptomatic or produce only mild symptoms. These cases play an essential role in spreading the virus and averting disease control. A further 14% exhibit severe symptoms, and 6% become critically ill[9]. Not all patients exhibit the same symptoms, with many developing a more severe form of the disease with additional complications, like pneumonia, acute respiratory distress syndrome (ARDS), shock, or acute kidney damage. These patients are characterized by poor health outcomes and high mortality rates[5]. Overall estimates suggest a case fatality risk (CFR) for COVID-19 of nearly 0.3-14.8%. In most of cases, fatality rate increases in patients who are older than 60 years or who have underlying significant comorbidities[3].

SARS-CoV-2 Structure and Cellular Tropism

SARS-CoV-2 shares the structural characteristics of the Coronaviradae family: an enveloped virion with positive-sense, single-stranded RNA genome. Surface projections appear as a halo (corona) surrounding the virus envelope, produced by glycoproteins. The virus contains four essential structural proteins. Three of them are viral surface proteins, namely spike glycoprotein (S), envelope protein (E), and membrane protein (M). These enclose the fourth nucleocapsid protein (N). Of the surface proteins, S is the most important, since it allows SARS-CoV-2 to interact with angiotensin-converting enzyme 2 (ACE2), a cell surface receptor that exists on epithelial cells of human respiratory system. Its two functions are mediated by two regions, S1 and S2. The host cell receptor binding is completed by S1, and the membrane fusion by S2[10].

Subsequent to S-ACE2 binding, S undergoes a conformational modification triggered by the S2 region exposing a cleavage spot mediated by proteolysis of endosomal pH-dependent cathepsin

L. Extracellular proteases excreted by neutrophils maintain this pathway sufficiently well to enable the virus to enter, and become adsorbed onto the cell surface[11].

Other cellular proteins may also facilitate its entry into the host cell. Dendritic cell-specific intercellular adhesion molecule-grabbing non-integrin (DC-SIGN or CD209), an expressed C-type lectin receptors on dendritic subtypes, help the virus to exploit dendritic cells as transport vehicles to disseminate the virus[12]. Another lectin (LSECtin), expressed in sinusoidal endothelial cells, is believed to attach to S and possibly will facilitate viral access into the liver and/or lymph nodes[13]. Based on SARS-CoV replication data, SARS-CoV-2 is expected to complete its replication process between 9-24 hours[14].

ACE2 is a metallopeptidase that had previously been identified as the functional receptor for SARS-CoV. SARS-CoV-2 docks on the ACE2 using a transmembrane protease serine 2 (TMPRSS2) for S protein priming and cleavage at the site S1/S2 hence it allows fusion between viral, and cellular membranes[15]. Possible targets of SARS-CoV-2 (where ACE2 is abundantly present in humans) include the lining epithelium of the lungs, intestines, heart, kidneys, brain, and testicles[16]. Neurotropic attack may occur after viremia and/or via local ascending infection through upper nasal transcribrial route that facilitates the entry of SARS-CoV-2 into the cerebrum[17].

Cellular tropism and the profile of replication kinetics induced by SARS-CoV-2 was assessed by Chu et al.[18]. Using different human and non-human cell lines, 11 out of 25 cell lines including Calu3, Huh7, Caco2, 293T, U251, VeroE6, FRhK4, LLCMK2, CRFK, RK-13, and PK-15) have been found to support SARS-CoV-2 replication. Upon utilizing human ACE2 as an entry receptor, Calu3 (pulmonary) cell line is highly permissive to SARS-CoV-2 and SARS-CoV that have the ability to cause pneumonia. In addition, SARS-CoV-2 replicated less efficiently than SARS-CoV in Caco2 (intestinal) cells supporting the high incidence of diarrhea in patients with SARS than in COVID-19 patients. Also both SARS-CoV-2 and SARS-CoV showed marked replication in Huh7 (hepatic cell) and 293T (renal cell) explaining the hepatic and renal damages in COVID-19. Other interesting finding shows that modest SARS-CoV-2 replication observed in U251 of a neuronal cell origin, might correlate to the development of various neurological manifestations in COVID-19 patients[18].

Route of Transmission and Viral Shedding

Human-to-human transmission takes place primarily through droplets expelled while coughing, sneezing, and talking. This form of contact is conducive to virus transmission because droplets pass directly from the infected human respiratory tract, seeding onto mucosal surfaces of the susceptible recipient, commonly within a circle with a radius of ≤91.4 cm around the patient. Reducing the risk of transmission through droplets requires facial protection (including the use of masks), especially for healthcare workers. More recently, such measures have been approved for use by the general public in high-risk areas[19]. Close contact contamination with an infected person is the most significant factor behind the global spread of SARS-CoV-2. Catching the virus from droplet-contaminated surfaces, objects or fomites, and then rubbing the eyes, scratching the nose or touching mouth are another possible entry route of the virus into a host[19].

Aerosol transmission may be plausible in specific clinical situations, settings where infected patients are treated as aerosols generated by procedures requiring suctioning, intubation, induction of cough, use of nebulizers, manual ventilation, change of the patient position, tracheostomy, and resuscitation in cardiopulmonary arrest[20].

A recent experimental study[21] argues that SARS-

CoV-2 can stay in the air for over three hours, survive on plastic and stainless steel surfaces for 2-3 days, and on cardboard for about 24 hrs. Survival time is dependent on the density of respiratory secretions, environmental conditions such as temperature and humidity, and the contagiousness of the virus over the distance travelled by droplets between the source and new potential host. Further research has shown that the mucous membranes in nasal cavity, conjunctivae, and less often the mouth are exposed portals of entry for respiratory viruses. Unlike most enveloped viruses, corona glycoproteins allow the virus to withstand gastrointestinal conditions in the digestive tract, making the spread of the virus possible through faecal-oral routes[22].

On the basis of existing clinical virological data, the infectious period is usually long for COVID-19, possibly extending for ten or more days after signs and symptoms of the disease appear[6,21]. To date, there has been no reported risk of COVID-19 transmission through vectors of human origin which include blood, blood components, human tissues, reproductive and non-reproductive related cells and organs. There are still, however, concerns that viremia can occur in the incubation period, throughout the pre-symptomatic period, or after the resolution of symptoms, with implications for safety practices[8].

The rates of viral transmission in pre-symptomatic phase has been recorded to be between 48% and 62%[23]. Until recently vertical transmission of SARS-CoV-2 has not been reported, although one case believed to be associated with perinatal transmission. In neonates, no severe negative outcomes have been observed due to maternal viral pneumonia[24].

Viral shedding plays a crucial role in circulating the virus among populations. Since viral shedding occurs primarily in asymptomatic or pre-symptomatic patients, it can make controlling the disease very difficult. Zhou et al.[25] reported that the average duration for viral shedding is (20 days) starting from the disease onset, and might be prolonged to 37 days. Viral shedding lasts for a median of 19 days among severely ill patients, and 24 days among critically ill patients. Viral RNA has been detected in respiratory samples, faeces, blood, serum, saliva and urine of symptomatic patients[8]. In addition, viral RNA has been identified in the tears and from conjunctiva of COVID-19 infected patients suffering from conjunctivitis[26]. High viral load is linked with severity of clinical illness. Viral shedding has not been detected in breast milk. Liu et al.[27] observed the shedding patterns of viral RNA in mild and severe cases of COVID-19. Patients with severe disease have around 60 times the viral load found in those with mild cases which are associated with severe clinical outcomes. Besides, early viral clearance among mild cases was found[27].

Tan et al.[28] reported a special case of prolonged viral shedding persisting for 49 days in a specimen collected through oropharyngeal swabs from a mildly infected patient. They concluded that the virus does not shed rapidly from infected human bodies[28]. In tandem with other data, this is suggestive of a relatively long viral shedding period in contrast to other respiratory viruses which complicates efforts to stop the viral transmission and suggests a need for mass vaccination.

SARS-CoV-2 Viremia

Local primary replication and cell-to-cell spread are the major goals of SARS-CoV-2, as its replication is limited to the upper part of the respiratory tract, while descending to the lung is determined by viral virulence and host susceptibility factors. Unsurprisingly, high viral load in nasal/throat samples is linked to high viral exposure, increased contagiousness to others, and more severe forms of disease and related complications[8,29,30].

It is well-established that most respiratory viruses attach locally to airway receptors, curtailing the

possibility of blood-borne transmission. Viremia that disseminates the virus throughout the body via the blood stream is found in a limited number of studies documenting the viral load of SARS-CoV-2 using blood or serum samples. In symptomatic COVID-19 cases, low levels of viremia have been detected[31]. Development of viremia during the incubation period, prodromal phase of infection and post-recovery period was uncertain until recently[8].

The peak level of viremia appeared to be delayed up to the end of the 14 days[22], raising the prospect that viral load may be high enough to maintain transmission for 1-2 days prior to disease onset[32].

Tissue Injury (Direct and Indirect)

Direct cell damage and induced apoptosis is mainly caused by virus replication. In general, the replication of coronaviruses in tissue culture is often associated with an inhibition of host protein synthesis, as described by Narayanan et al.[33] Notably, it was determined that non-structural protein 1 (NSP1), the N-terminal PP1A (1ab-derived processing product), plays a vital role in suppressing host translation and is able to suppress the expression of host gene in a variety of ways[33]. In 2009 study by Kamitani et al.[34] on SARS-CoV indicated that translation of host mRNA was prohibited and degraded after NSP1 binding to 40S ribosomal subunit[34].

Direct cell injury is also inflicted through the inhibition of interferons with known antiviral properties. This phenomenon has been clearly explained in Spiegel M et al.[35] who found that SARS-CoV virus seems to block the activity of interferons immediately after an early nuclear import of the transcription factor interferon regulatory factor 3 (IRF-3), which is essential for the activation of IFN-β promoter, inhibiting the activation of the interferon system. Other studies have demonstrated that nucleocapsid (N-proteins) present in SARS-CoV and MERS-CoV inhibit the release of Type I interferons by a different mechanism, namely by suppressing the ubiquitination and expression of Retinoic acid-Inducible Gene I (RIG-I)[36].

Cytopathic effects are found particularly in the alveolar epithelium. Park et al.[37] succeeded in isolating the virus on various cell lines, in the first Korean patient infected with COVID-19. These cell lines included human airway epithelium, Vero E6 and Huh-7 cell cultures. The cytopathic effects of the virus, including cell rounding, refractile appearance, and cell detachment, were observed three days after the initial blind passage of the oropharyngeal sample[37].

A histological examination of post-mortem lung tissues demonstrated bilateral lesions of diffuse alveolar insult with cellular fibromyxoid plugs, evidence of pneumocytes desquamation, formation of hyaline membrane and pulmonary edema. These observations are indicative of ARDS. Lung tissues were also infiltrated by interstitial mononuclear inflammatory cells, predominantly with lymphocytes[38]. Viral cytopathic-like changes were also identified in the alveolar spaces of multinucleated syncytium with abnormal giant pneumocytes, featured as a large nuclei with prominent nucleoli and amphophilic granules in the cytoplasm. Abnormal pneumocytes often indicate the presence of an alveolar damage[38]. Any obvious nuclear or cytoplasmic viral inclusions were not identified[38].

Indirect cell damage is triggered by induced inflammation and accentuated by immunological attack. The key factors in the immunopathogenesis are atypical responses and cellular damage in the immune system. During the course of illness, numerous organs and cell types can become infected and suffered from indirect injury, including intestinal mucosal cells, epithelial cells in the kidneys tubules, neuronal cells in the brain, and any other immune cells[38]. Other factors include the dysregulation of cytokines

and chemokines, a defect in the innate immune system, direct effects of viral infection on immune cells, severe downregulation or absence of lung protective angiotensin-converting enzyme 2, autoimmunity, and genetic factors[38]. An autoimmune response akin to that observed with SARS may be implicated in pathogenesis. Indeed, Lin et al.[39] showed that antibodies against S2 glycoprotein in convalescent sera of SARS infected patient were cross-reacted with lung epithelia, and enhanced adhesion of immune cell to lung epithelium, causing cytotoxic damage to type-2 pneumocytes. This suggests that using steroids and plasmapheresis trials to correct these immune-pathogenic mechanisms may be a promising approach to treating SARS-CoV[39]. Meanwhile, the FDA is facilitating access to antibody-rich plasma of patients recovered from COVID-19. Despite many clinical trials, there are some limitations for using convalescent plasma, as it has not yet been proven to be effective and specific in COVID-19 since it is important to determine its safety and efficacy before routine administration to patients with COVID-19[40].

Immune Evasion

Viral immune evasion is the process by which viruses escape the host immune system using various strategies to circumvent and antagonize the host immune response. The ultimate consequence of this battlefield is a major determinant of the pathogenesis of the viral infection[37]. SARS-CoV-2 has learned how to evade immune system by different strategies. As noted in previous publications on SARS-CoV, immune response can - as observed in other viruses[41] - be suppressed through intracellular antiviral response abrogation, aptly described by Kurg et al.[42] as "intracellular warfare"[42]. A study by Samuel et al. has shown that an antiviral protein called the Myxovirus Resistance Protein A (MxA) that is triggered by interferon α and β, acts against wide range of viral RNA. Even though the MxA is well expressed in Vero cultures of SARS[41] it does not inhibit virus replication, suggesting that SARS-CoV is able to counter this antiviral defence system[43].

Another explanation for immune evasion by corona virus, put forward by Gu et al.[44] revealed that the adaptive immune system is itself a target for viruses, citing examples of CD4+ and CD8+ lymphocytes infected directly by the virus. Similarly, Chen et al.[45] identified the cause of lymphopenia in a SARS-infected patient as virus-induced apoptosis of lymphocytes. Other studies have profiled multiple toxic viral molecules implicated in lymphocyte apoptosis, including E protein, U274, U154, U122 and S[46].

Chinese scientists investigated SARS virulence and its immune escape mechanisms by comparing protein motifs of SARS-CoV with other known proteins expressed both in human beings and the virus. They found that toxic motifs localized to most of SARS-CoV proteins might be an appropriate focus of treatment and vaccine design[47]. For instance, toxic behaviour of these motifs appeared in S, E, N, and some other accessory proteins acting as superantigens that may cause lymphocyte apoptosis through massive recruitment and stimulation, lacking proper costimulatory signals. Whereas motif in S protein that acts as an enterotoxin could explain the diarrhea seen in a number of SARS sufferers[47].

A recent study by Chu et al.[48] has assessed the ex-vivo susceptibility of human lung tissues to both SARS-CoV-2 and SARS-CoV, found that despite the elevated viral load of SARS-CoV-2, the virus did not stimulate the secretion of interferon, and it was also associated with down-regulation of proinflammatory cytokines compared to SARS-CoV, suggesting another mechanism of SARS-CoV-2 immune evasion.

Cytokine Storm Syndrome in COVID-19

Accumulating evidence indicates that immunological hyperactivation in the form of a

cytokine storm which termed as a macrophage activation syndrome (MAS) or secondary hemophagocytic lymphohistiocytosis (sHLH), contributes to disease severity and increases the risk of death in heavily-affected COVID-19 patients[7,9,49,50]. A timely and well-orchestrated innate immune response is crucial for the effective resolution of CoV infections. During a cytokine storm, the immune system's precision is lost, leading to the overproduction of proinflammatory cytokines that can cause significant cellular damage[51]. In a prospective study by Huang et al.[49], the authors sought to compare the cytokine profiles of COVID-19 patients that were admitted to the intensive care unit (ICU) to those in non-ICU treatment. A statistically significant elevation in the plasma levels of interleukin 2 (IL2), IL7, IL10, granulocyte colony-stimulating factor (G-CSF), interferon γ-induced protein 10 (IP10), tumour necrosis factor α (TNFα), macrophage inflammatory protein 1α (MIP1α), and monocyte chemoattractant protein 1 (MCP1) was detected in ICU patients, compared to their non-ICU counterparts[49]. Blood samples of all 41 patients involved in this study were collected over a median of four days after hospitalization (range: 2-5 days), indicating that these differences in immunological profile can be observed during the acute phase of the disease[49]. The authors concluded that the SARS-CoV-2-mediated cytokine storm observed exclusively in ICU patients might correlate with disease severity and outcomes of this subset of patients[49].

To further investigate the immunopathologic mechanisms behind the SARS-CoV-2 infection, retrospective data from 21 patients with COVID-19 were analysed by Chen et al.[7]. In the study, patients were categorized as "moderate" or "severe" based on their oxygen saturation, respiratory rate and need for mechanical ventilation. Significantly elevated levels of lactate dehydrogenase (LDH), high-sensitivity C-reactive protein (hsCRP), and ferritin were detected in patients with severe COVID-19, as compared to moderate cases which were indicative of systemic hyperinflammation[7]. To address the possibility of a cytokine storm present in severe cases, the authors measured the levels of multiple cytokines upon patient hospitalization. Interestingly, patients with severe COVID-19 had higher serum concentrations of the proinflammatory mediators IL2 receptor (IL2R), IL6, IL10, and TNFα, as compared to moderate cases. Notably, IL6 was markedly increased in both moderate and severe cases while IL1β, a key proinflammatory player in SARS-CoV immunopathology[52], was undetectable in all patients[7]. Further immunological analysis suggested that SARS-CoV-2 induced more marked CD4 and CD8 T-cell lymphopenia in severe cases, as well as more significant suppression of CD4 T-cell-mediated INF-γ production[7]. These findings were supported by those in a smaller study performed by Zheng et al.[53]. Taken together, these results are suggestive of a SARS-CoV-2-mediated cytokine storm in a subset of COVID-19 patients, which appears to be correlated with disease severity and poor clinical presentation.

In an attempt to pinpoint the exact sources of SARS-CoV-2-induced cytokine storms and their role in disease progression, Yang et al.[54] examined a panel of 48 cytokines in 53 patients with either moderate or severe COVID-19. Of those, 14 cytokines were significantly increased in all COVID-19 cases as compared to control groups, including INF-γ, IL1Rα, IL2Rα, IL6, IL10, IL18, hepatocyte growth factor (HGF), monocyte chemotactic protein 3 (MCP3), monokine-induced γ interferon (MIG), G-CSF, macrophage-CSF (M-CSF), IP10, MIP1α, and cutaneous T-cell attracting chemokine (CTACK)[54]. Moreover, the authors compared the cytokine profiles of moderate and severe cases upon hospital admission and at a later stage (≥15 days after disease onset). While most of the aforementioned COVID-19-associated cytokines were recorded at similar levels in both groups, and at both points of measurement, cytokines IP10, MCP3, and IL1Rα were found to be significantly higher in severe

cases. Spearman's rank coefficient correlation analysis showed that all three cytokines were highly associated with arterial partial oxygen pressure (PaO_2) / inspired oxygen fraction (FiO_2) levels and Murray ARDS scores, while IP10 alone was found to be correlated with viral load[54]. Lastly, the authors showed that IP10, MCP3, and IL1R1α measurements in combination, could be used as prognostic marker for COVID-19 clinical outcomes (ROC/AUC 0.943)[54].

Although further clinical trials are needed to fully map the immunological modulators involved in SARS-CoV-2 infection, it is evident that host immunity hyperactivation in the form of cytokine storms plays a key role in the pathogenesis, and especially in the disease severity of COVID-19. This feature of hyperinflammation, observed in critically ill patients, provides a promising target for COVID-19 therapeutic research. Indeed, preclinical data have shown that immunomodulatory agents, like the TNFα and IL6 suppressor, hydroxychloroquine, as well as corticosteroids[50,54] may be useful in controlling the SARS-CoV-2-associated cytokine storm and alleviating disease symptoms[55].

Antibody-Dependent Enhancement

The immunopathology of antibody-dependent enhancement (ADE) has been studied in certain viruses, allowing them to utilize their ability to neutralize antibodies, and to promote their entry into host cells. In most cases, these viruses exploit FcR expressed on phagocytes to enable them to replicate in macrophages and monocytes, subsequently harnessing them to reach body tissues. This phenomenon is known as "ADE of virus infection" or "immune enhancement of disease."[56]. It is well known that antibodies target one serotype of viruses, excluding others, in order to subneutralize it, resulting in ADE of the subsequent viruses. A neutralizing antibody attaches itself to coronaviral surface protein(S), and behaves as a viral key receptor facilitating the entry of the virus into IgG- Fc receptor complex expressed on host cells through viral receptor-dependent pathways. The impact of antibody dose on viral fusion into cells expressing viral receptor, Fc receptor, or both receptors, have been extensively evaluated by Wan et al.[57]. The authors showed that antibodies play complex roles in viral entry and can play a role in guiding future vaccine design and antibody-based therapeutics for COVID-19. Moreover, a study focusing on MERS[57] investigated the impact of a neutralizing monoclonal antibody (MAb) using pseudo-virus entry and biochemical assays on the receptor binding domains (RBD) of S proteins. In the meantime, MAb attaches to the IgG-Fc receptor on the cell surface, guiding viral entry suggesting that the antibody/Fc-receptor complex functionally resembles the viral receptor encountered in viral entry. Further, the study has delineated MAb usage guidelines in managing viral diseases, potentially identifying a novel molecular system for antibody enhancement during viral access, and promising avenues for vaccine preparation and antiviral strategies to pursue.

In two recent studies on samples of 222 and 173 infected cases with COVID-19, respectively[58,59], both antibodies of class IgM and IgG specific to SARS-CoV-2 were detected. The studies also found that an increased IgG response and high antibody titres were associated with disease severity, and induction of a severe inflammatory response, raising the possibility of ADE in COVID-19 infections. Data from other studies also support the ADE hypothesis, indicating that disease severity could be associated with the appearance of neutralising antibodies between day 7-10[60].

The potential pathogenic consequences of using antibodies targeting COVID-19 virus present an important and concerning challenge to the development of vaccines and antibody-based treatments. Further studies should be conducted on large-scale cohorts to prove or reject this possibility.

CONCLUSIONS

The battle against COVID-19 is not yet over, and many unmet challenges remain for healthcare workers, researchers and above all those at risk of infection and disease. The COVID-19 crisis is ongoing, and will continue to cause more deaths worldwide. The lessons from SARS-CoV have not been learned, with healthcare systems around the world were not prepared to face the current wave of infection, or re-emergence of infections in the future. Given that there is currently no proven specific anti-COVID-19 treatment, further research is needed to fully understand the pathogenesis of SARS-CoV-2.

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